

Phytochemistry, pharmacology, and therapeutic uses of black seed (*Nigella sativa*)

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[ABSTRACT] Black seed (*Nigella sativa*) is an annual flowering plant from Ranunculaceae family, native to southwest Asia. This plant has many food and medicinal uses. The use of its seeds and oil is common for treatment of many diseases, including rheumatoid arthritis, asthma, inflammatory diseases, diabetes and digestive diseases. The purpose of this study was to provide a comprehensive review on the scientific reports that have been published about *N. sativa*. The facts and statistics presented in this review article were gathered from the journals accessible in creditable databases such as Science Direct, Medline, PubMed, Scopus, EBSCO, EMBASE, SID and IranMedex. The keywords searched in Persian and English books on medicinal plants and traditional medicine, as well as the above reputable databases were "Black seed", "*Nigella sativa*", "therapeutic effect", and "medicinal plant". The results showed that *N. sativa* has many biological effects such as anti-inflammatory, anti-hyperlipidemic, anti-microbial, anti-cancer, anti-oxidant, anti-diabetic, anti-hypertensive, and wound healing activities. It also has effects on reproductive, digestive, immune and central nervous systems, such as anticonvulsant and analgesic activities. In summary, it can be used as a valuable plant for production of new drugs for treatment of many diseases.

[KEY WORDS] *Nigella sativa*; Black seed; Medicinal plant; Ethnopharmacology; Phytotherapy

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Introduction

The use of medicinal plants has been considered for the treatment of human diseases since ancient times. Medicinal herb is a plant that is able to change the physiological and pathological processes and can be used to prevent or treat diseases. In recent years, there is a significant increase in the use of medicinal plants, compared with the chemical drugs, due to several factors, such as easy access without prescription, low-cost, no need to refer to healthcare professionals, as

well as believing in fewer side effects for the treatments with natural products.

The world health organization has estimated that about 80% of people benefit from herbal remedies. Therefore, it is necessary to evaluate the rich heritage of traditional medicines; however, only a few number of plant species have been thoroughly studied for therapeutic properties, mechanism of action, safety and toxicity; so many researches on medicinal plants are to be done. In Iran, medicinal plants have been frequently used in traditional medicine [1-5]; in addition, most of them have been investigated for treatment of different diseases such as gastrointestinal diseases [6], headache and migraine [7], fertility [8-9], diabetes [10], hyperlipidemia [11-13], renal injury [14], stress and depression [15-16], pain [17], respiratory diseases [18], neurological disorders [19], liver disorders [20-21] and cancers [22-25].

Out of the medicinal plants, black seed (*Nigella sativa*), which is native to southwest Asia and has a rich historical and

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cultural heritage, due to a wide range of medicinal properties, is widely used in Iran [26-27]. *N. sativa* seeds have been used to promote health and fight diseases, especially in the Middle East and Southeast Asia [28]. *N. sativa* in South Asia is known as Kalonji, in Arabic as *Habbat-ul-Sauda*, and commonly referred as black cumin in English [29].

Botanical characteristics

N. sativa belongs to Ranunculaceae family and is an annual herbaceous plant which mainly grows in various parts of southern Europe and some parts of Asia [30], including Syria, Turkey, Saudi Arabia, Pakistan and India [31].

Flowers are elegant predominantly white, yellow, pink, light blue or lavender and have 5–10 petals. The fruits of this

plant are large and swollen capsule, which contain numerous black seeds with aromatic and bitter taste [26] (Fig. 1).

N. sativa cultivation time is usually between November and April and germination lasts for about 10–15 days after sowing seeds. The flowering and fruiting times of the plant are generally from January to April [32].

Scientific classification of the plant

Kingdom: Plantae
Division: Magnoliophyt
Order: Ranunculales
Family: Ranunculaceae
Genus: *Nigella*
Species: *sativa*



Fig. 1 *Nigella sativa*

Chemical composition of *N. sativa*

So far, several chemical compounds have been extracted and identified from different species of *Nigella* [33]. *N. sativa* contains 216 g protein, 406 g fat, 45 g ash, 84 g fiber, 249 g free nitrogen extract, 38 g moisture, 105 mg iron, 18 mg copper, 60 mg zinc, 527 mg phosphorus, 1 860 mg calcium, 15.4 mg thiamin, 57 mg niacin and 160 µg folic acid per kg [34]. Also, studies have shown the presence of different active pharmaceutical ingredients in the *N. sativa* seeds, including thymoquinone, thymol, limonene, carvacrol, *p*-cymene, alpha-pinene, 4-terpineol, longifolene, and *t*-anethole benzene [35-37].

Moreover, other phytochemical studies have revealed that the plant seeds contain two classes of alkaloids, including isoquinoline alkaloids such as nigellimine-N-oxide, and pyrazole alkaloids such as nigellidine and nigellicine [38-40]. *N. sativa* seeds are also rich in unsaturated fatty acid such as linoleic acid, oleic acid, and palmitic acid [41]. Other components of the seeds include saponins, flavonoids, indazole-type alkaloids, cardiac glycosides, vitamins, and some important minerals like calcium, phosphorus and iron [42-43]. Some main constituents of *N. sativa* seeds with chemical structures are shown in Fig. 2.

Use of *N. sativa* in traditional medicine

Food and therapeutic uses of *N. sativa* oil (NSO) and seeds have a long history in Indian and Arabic culture. *N. sativa* has been traditionally used for treatment of various

diseases (e.g., asthma, bronchitis, rheumatism, headaches, and dysentery) in Southeast Asia, Northern Africa and Middle East [44]. According to recent reports the grain's syrup was beneficial for digestion, appetite loss, amenorrhea, and dysmenorrheal and treatment of worms and skin rash [45].

Avicenna in his famous book, Canon of Medicine, has pointed out several black cumin properties, such as fatigue improvement and energy recovery. Islamic medicine also has enlisted health effects for this plant [46].

Pharmacological potentials

Anti-microbial activity

Experimental studies have reported that NSO and *N. sativa* extracts have anti-microbial activity against a wide range of microbes, especially multiple-antibiotic resistant bacteria [47-48]. Anti-microbial effects of the plant extracts have been determined in Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) and the pathogenic fungus *Candida albicans* [49]. It is found that anti-microbial properties of *N. sativa* are due to its active compounds such as thymohydroquinone and melanin [42]. Evaluation of *in vitro* anti-bacterial activity of NSO on pathogenic bacteria species consisting of three gram-positive, eleven gram-negative and *C. albicans* yeast has indicated strong sensitivity in all species [50]. Researchers have shown that *N. sativa* extract could effectively eradicate non-lethal staphylococcal infection in mice after subcutaneous injection [49].

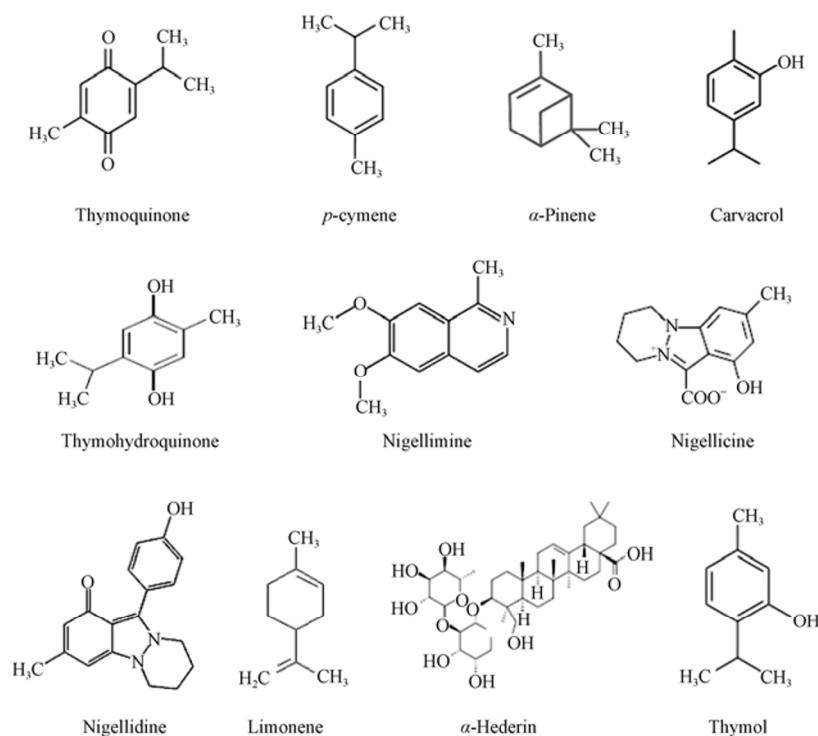


Fig. 2 Chemical structures of some main constituents of *Nigella sativa* seeds

Experimental studies have revealed that *N. sativa* extracts have synergistic effects on eradication of *E. coli* together with antibiotics such as gentamicin, streptomycin, doxycycline, chloramphenicol, ampicillin, nalidixic acid, terbinafine, and cephalexin [49, 51]. Also, *N. sativa* has inhibitory effects on the growth of bacteria such as *Yersinia enterocolitica*, *Listeria monocytogenes*, *Corynebacterium pseudotuberculosis*, *Corynebacterium renale*, *Brucella abortus*, *Pasteurella multocida*, *Mannheimia haemolytica*, *E. coli*, *Trueperella (Arcanobacterium) pyogenes*, and *S. aureus* [52].

Another study has shown that NSO has anti-staphylococcal effect comparable with antibiotics such as ceftazidime, cefuroxime, cefaclor, and cefamandol [53]. Moreover, *N. sativa* methanolic extract shows the strongest anti-fungal effect. It exhibits inhibitory effect against candidiasis in mice [54]. In a study antidermatophyte activity of *N. sativa* ether extract and thymoquinone (TQ) was examined against eight species of dermatophytes: four species of *Trichophyton rubrum* and one each of *Trichophyton interdigitale*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum* and *Microsporum canis* [55]. In another study the anti-oxidant and anti-schistosomal activities of the garlic extract (GE) and NSO were considered. The results have demonstrated that, protection with GE and NSO significantly ameliorate the anti-oxidant capacity of schistosomiasis mice compared to the infected-untreated ones and prevent most of the hematological and biochemical changes [56]. Also, Mahmoud *et al.* have studied the effects of NSO in liver damage induced by *S. mansoni* infection in mice. Infection with *S. mansoni* produces

a pronounced elevation in the mouse serum activity of ALT, GGT, with a slight increase in AP level, while reducing serum albumin level and administration of NSO succeeds to correct the changes in ALT, GGT, AP activity, as well as the Alb content in serum [57].

Anti-oxidant activity

In several studies, anti-oxidant activity of *N. sativa* seeds has been reported. *N. sativa* could be a useful compound for preventing and treating cerebral ischemic and neurodegenerative diseases, due to its anti-oxidant property [58]. Co-administration of NSO with cisplatin in male rats improves oxidative stress induced by cisplatin in testicles [59]. Also in a study to determine the anti-oxidative properties of *N. sativa*, 64 healthy subjects received 3 g *N. sativa* daily for two weeks. The results indicated a significant reduction in lipid peroxidation after consumption, and therefore the anti-oxidant activity of *N. sativa* was confirmed in that study [60].

N. sativa extract consists of numerous anti-oxidant compounds, including TQ, carvacrol, *t*-anethole and 4-terpineol [61]. TQ with powerful anti-oxidant properties indirectly reduces the production of reactive oxygen species and causes the inhibition of lipid peroxidation [62-63]. NSO or TQ injection in ischemia phase causes reperfusion and improves the performance and level of glutathione peroxidase and superoxide dismutase in rats [64]. TQ improves non-enzymatic (GSH and vitamin C) and enzymatic activities (SOD, CAT, GPX, and GST) of anti-oxidants. It also reduces malondialdehyde (MDA) to normal in mouse brain [65]. In another research, TQ modulatory effects on erythrocyte lipid peroxida-

tion and anti-oxidant status are elevated during 1, 2-dimethylhydrazine-(DMH)-induced colon carcinogenesis in male rats. Also, TQ pre-treatment improves increased level of MDA and conjugated diene levels to normal and reduced increment of enzyme activities like CAT, glutathione peroxidase, and SOD activities^[66]. Moreover, treatment effects of TQ on arthritis in rats are determined by biochemical assays, demonstrating that TQ causes significant changes in all parameters (articular elastase, MPO, LPO, GSH, CAT, SOD and NO)^[67]. Indeed, NSO and TQ inhibit lipid peroxidation in liposomes, via a non-enzymatic way^[50].

Other compounds of NSO like quinone, carvacrol and 4-terpineol are wonderful in connecting free radicals to each other for neutralization^[68]. These compounds have been evaluated in many *in vitro* anti-oxidant tests. The results indicate that different combinations of *N. sativa* have synergistic effects. The combination of *N. sativa* with iron prevents oxidation. In many diseases, such as cirrhosis or liver damage, *N. sativa* anti-oxidant activity could eliminate free radicals^[69]. Also in a phytochemical research on hydroalcoholic extract of Khorasan *N. sativa* species, it has compounds such as tannin (3+), flavonoids (+) and alkaloids (2+)^[70]. Among the flavonoids, aglycones and flavonol glycosides are also present in the *N. sativa*. These flavonoids have higher anti-oxidant effects and consequently a more anti-radical effect, so they act as a revealer of superoxide radicals in the blood to eliminate free radicals and inhibit the oxidation process in cells^[71-72].

Anti-inflammatory activity

In traditional medicine, fixed oil of *N. sativa* seed is widely used to treat skin rashes, back pain, rheumatism, and related inflammatory diseases. Studies have shown that fixed oil of black cumin seed and TQ exert their anti-inflammatory properties by inhibiting the production of these compounds^[68, 73]. Eosinophils, oxidants, cytokine, and inflammatory macrophages and neutrophils are responsible for creating inflammation condition in body^[74]. It is found that administration of aqueous extract of *N. sativa* or TQ in calcium ionophore-stimulated neutrophils inhibits production of 5-lipoxygenase^[73].

Anti-inflammatory effects of NSO and TQ have been shown in several inflammatory models of experimental encephalomyelitis, colitis, peritonitis, arthritis and edema, which mediate inhibition of inflammatory mediators, prostaglandins, and leukotrienes^[75]. Also the anti-inflammatory effects of TQ and *N. sativa* extract on LPS-induced inflammation in the mix-glial cells and macrophages indicate a reduction in nitric oxide production by these cells^[76], which is probably due to the inhibition of iNOS by TQ^[77].

Moreover, anti-inflammatory potential of TQ in PDA cells is compared with trichostatin A, a specific inhibitor of histone deacetylase (HDAC). TQ considerably reduces synthesis of MCP-1, TNF- α , interleukin (IL)-1 β and Cox-2 in PDA cell dose- and time-dependently. TQ affects p21 WAF1 expression, inhibits HDAC activity and induces histone

hyperacetylation, so TQ suppresses inflammation associated cancer, through HDAC inhibition^[78]. TQ affects adenosine receptors, which suggests that some of its anti-inflammatory effects may be mediated by these receptors^[79]. In another study, the antiasthmatic (bronchodilatory) effect of *N. sativa* extract in asthmatic patient airways was examined and the results showed that the extract caused significant increase in all pulmonary function tests^[80].

Anti-hyperlipidemic activity

N. sativa has significantly improved the lipid profiles in menopausal women [decreased total cholesterol, low density lipoprotein cholesterol (LDL-c) and triglyceride (TG), and increased high density lipoprotein cholesterol (HDL-c)] more than the placebo treatment within two-month intervention. One month after discontinuation of treatment, the lipid profiles in the *N. sativa*-treated group have changed towards the pretreatment levels^[81]. In another study, the effect of *N. sativa* seeds has been evaluated on lipid profile in patients with type 2 diabetes. The results have shown that patients ingested 2 g·d⁻¹ *N. sativa* display a significant decline in TC, TG, and LDL-c, and a significant elevation in HDL-c/LDL-c, compared with their baseline data and control patients. But increasing *N. sativa* dose to 3 g·d⁻¹ has failed to show any increase in the hypolipidemic effect produced by the 2 g·d⁻¹ dose^[82]. Amini *et al.* have studied the potential hypolipidemic effects of the NSO on healthy volunteers. Their results have shown significant decreases in fasting blood cholesterol, LDL, triglyceride, glucose and HbA1C levels in NSO treated volunteers, as compared to placebo group at the end of the study^[83]. Also Bano *et al.* have investigated the effects of aqueous extract of *N. sativa* seeds on body weight, food intake, and some biochemical parameters in rats. Their results show that *N. sativa* decreases body weight and food intake with no decrease in water intake. Blood glucose, serum cholesterol, TG and low density lipoproteins (LDL) are significantly decreased and HDL significantly increased^[84].

Anti-cancer activity

N. sativa seed, its essential oil and some of its active compounds, especially TQ and α -hederin, have been shown to exert significant anti-cancer effects on a variety of neoplasms^[43]. For *N. sativa* anti-cancer effects, different mechanisms such as utilization of free radicals, effects on enzyme activity, inhibition of cell proliferation^[85], changes in intracellular glutathione, anti-oxidant activity, trapping free radicals^[59, 86] and induction of apoptosis in cancer cells through a pathway dependent and independent of p53 have been proposed^[87]. Also for TQ anti-cancer mechanism, its effects on colon cancer cells are growth inhibition, morphological changes and increased apoptosis of cancer cells. TQ induces apoptosis by increasing the expression of the target gene mRNAs of P53 and p21WAF1 and inhibition of anti-apoptotic proteins (BCL-2)^[88]. In a study, the methanol extract of *N. sativa* shows a strong cytotoxic action against *Ehrlich ascites* carcinoma cells and Dalton's ascitic lymphoma cells and a minim-

al cytotoxicity to normal lymphocytes^[89]. Cytotoxic and apoptotic effects of *N. sativa* ethanol extract on ACHN line of renal cancer cells in comparison to normal L929 cells have been reported^[90]. *N. sativa* seed extract has potent anti-cancer effects on sarcoma and lymphoma-180 cells, with less toxicity on normal lymphocytes^[91]. Also topical application of *N. sativa* extract inhibits early stages of skin cancer in mice^[92]. Moreover, TQ anti-tumor and anti-angiogenic effects on osteosarcoma *in vitro* and *in vivo* have been investigated and the results demonstrate that TQ induces a higher percentage of growth inhibition and apoptosis in the human osteosarcoma cell line SaOS-2 and blocks constitution of human umbilical vein endothelial cell tube in a dose-dependent manner. It is observed that TQ significantly downregulates NF- κ B DNA-binding activity, XIAP, survivin, and VEGF in SaOS-2 cells. Treatment with TQ upregulates cleaved caspase-3 and SMAC in SaOS-2 cells. TQ effectively inhibits tumor angiogenesis and tumor growth both *in vitro* and *in vivo*. As a result, inhibition of NF- κ B and downstream effector molecules is a possible mechanism of action for TQ's anti-tumor and anti-angiogenic activity in osteosarcoma^[92]. The inhibitory effects of TQ are reported *in vitro* and *in vivo* on benzo[a]pyrene induced stomach cervical cancer in rats^[93]. Another study shows that induced fibrosarcoma can be inhibited by TQ *in vitro* and the mechanism for this effect is not clear, but may be related to interference with DNA synthesis, which is probably related to glutathione reduction and storage, lipid peroxides, and the activity of some enzymes^[94-95].

Anti-diabetic activity

N. sativa has been recommended by many traditional medicine experts to treat diabetes^[96]. Significant effects of *N. sativa* on blood sugar reduction have been confirmed, which is probably due to the presence of essential oil^[42]. It is thought that the anti-diabetic properties of *N. sativa* are induced by activation of adenosine monophosphate kinase (AMPK), affecting cellular uptake of proteins with hypolipidemic and anti-diabetic properties^[97-98]. Oral administration of volatile oil of black cumin (2 mg·kg⁻¹·BW⁻¹) shows a significant reduction in blood glucose in Balb/c mice^[44]. Intraperitoneal injection of NSO (50 mg·kg⁻¹) caused considerable hypoglycemic effect in fasting normal rabbits and alloxan-diabetic rabbits. Because of no change in basal insulin levels in all groups, it appears that *N. sativa* reduces blood glucose by an insulin-independent mechanism^[99]. *N. sativa* extract show an insulin-sensitizing action by enhancing ACC phosphorylation, a major component of the insulin-independent AMPK signaling pathway, and by enhancing muscle Glut4 content^[100].

Moreover, *N. sativa* extract causes regeneration and relative proliferation in beta cells and a decrement in free radicals production in streptozotocin-diabetic rats^[101-102]. Treatment with *N. sativa* extract and oil and TQ, significantly decreases tissue MDA and serum glucose and increases serum insulin and tissue SOD levels in rats. These findings demonstrate

that *N. sativa* and TQ could be clinically useful in the treatment of diabetes and in the protection of β -cells against oxidative stress^[103]. In another research, *N. sativa* powder (mixed with edible food) and TQ (in drinking water) were given to rats for 25 days and hematologic parameters analysis demonstrated that TQ and *N. sativa* induced a significant decrease in blood sugar in normal rats^[104]. *N. sativa* extract consumption for two months in rabbits causes a considerable reduction in blood glucose and ceruloplasmin and improves histological and biochemical signs of liver injury. These beneficial effects can be attributed to its anti-oxidant properties^[105]. *N. sativa* regulates activity of glucose metabolism liver enzymes and thereby reduces gluconeogenesis. It inhibits the activity of glucose 6-phosphatase and fructose 1,6 bisphosphatase, which is involved in gluconeogenesis. Furthermore, *N. sativa* increases the enzyme activity of glucose 6-phosphate, which is involved in the pentose phosphate pathway in cells^[106-107].

Cardiovascular-protective activity

In a study, the protective effect of *N. sativa* on the thoracic aorta contractile response is evaluated in an experimental model of diabetes mellitus in rat. The results show that treatment of diabetic rats with this plant causes maximum reduction in contractile response to non-specific KCL agonist and specific noradrenaline agonist. Probably long-term oral administration of *N. sativa* could reduce vascular contractile responsiveness and the number of cardiovascular complications in diabetes^[108].

In another study, the effect of *N. sativa* is studied on cardiac activity in diabetic rabbits and results show that *N. sativa* extract modulates irregular heart activity in diabetic rats^[109]. The protective effects of TQ and acute (at 4 and 18 h) effects of diesel exhaust particles (DEP) on cardiopulmonary parameters in mice are investigated and the results indicate that TQ pretreatment causes systolic blood pressure reduction and prevents leukocytosis and IL-6 increment and decreases plasma SOD activity. It also inhibits reduction in platelet numbers and the prothrombotic events^[110]. Moreover, the effects of NSO on homeostasis, cholesterol and blood glucose levels have been investigated in rats and the results demonstrate decreases in serum cholesterol, TG, glucose and increases in leukocytes, platelets, hematocrit, and hemoglobin. *N. sativa* extract administered at a dose of 800 mg·kg⁻¹ for 12 weeks improved cardiac tissue damage caused by ischemia-reperfusion which was probably due to the anti-oxidant properties of *N. sativa*^[111]. Injection of essential oil component at 4–32 μ g·mL⁻¹ in anesthetized rats caused reduction in blood pressure and heart rate in a dose-dependent manner, which was inhibited by anticholinergics^[112]. In another experiment, dichloromethane *N. sativa* extract (0.6 mL·kg⁻¹·d⁻¹) reduced mean blood pressure in spontaneously hypertensive rats^[113].

Gastro-protective activity

In an experiment the anti-ulcer potential of *N. sativa* aqueous suspension is assessed on induced gastric ulcers and basal gastric secretion in rats and the results show that an

aqueous suspension of *N. sativa* inhibits induced gastric ulcer formation. This extract also significantly ameliorates the ulcer severity and basal gastric acid secretion in pylorus-ligated Shay rats. The anti-ulcer effect of *N. sativa* is possibly because of prostaglandin-mediated and through its anti-oxidant and anti-secretory activities [114]. It is also reported that *N. sativa* aqueous extract reduces indexes to 36% in aspirin-induced stomach ulcer in rats [115]. The use of NSO at a dose of 0/88 g·kg⁻¹·d⁻¹ for two weeks increases mucin and glutathione levels in stomach and decreases the amount of histamine. The protective effects of hydroalcoholic extract on the gastric mucosa have been demonstrated [116]. In a study, TQ (doses of 50 and 100 mg·kg⁻¹) and *N. sativa* are shown to have protective effects on gastric ulcer in Wistar rats, via their anti-oxidant effects, decreasing induced ischemia-reperfusion and gastric ulcer [117]. Moreover, TQ administration could prevent and improve colitis, which could be a therapeutic agent for the treatment of patients with inflammatory bowel disease [118].

Nephro-protective activity

A study has been carried out to show the possible beneficial effects of TQ in STZ-induced diabetic rats and to determine the predictive value of mesenchymal and epithelial markers in the response of diabetic nephropathy to TQ. TQ shows protective effects on experimental diabetic nephropathy. Both mesenchymal and epithelial markers serve as excellent predictors of early kidney damage and indicators of TQ responsiveness in STZ-induced diabetic nephropathy [119]. NSO enhances the hepato-renal protection mechanism, reduces disease complications and delays its progression [120]. *N. sativa* at different doses for five-week period shows no toxic effect on kidney function [121]. Moreover, another study was done to observe the nephro-protective effect of anti-oxidants, vitamin C and NSO. The results demonstrated that vitamin C and NSO both had nephro-protective effects. These two anti-oxidants, as combined, proved to have synergistic nephro-protective effects [122]. In another study, NSO (5.0 mL·kg⁻¹) pretreatment significantly decreased plasma transaminase activities, hepatic MDA, and TG levels with amelioration in hepatic histopathological findings [123].

Hepatoprotective activity

It has been reported that *N. sativa* (0.2 mL·kg⁻¹) intraperitoneally relieves the detrimental effects of ischemia-reperfusion injury on liver. *N. sativa* treatment protects the rat liver against hepatic ischemia-reperfusion injury [124]. TQ protective role in the hepatotoxicity of Cd⁺⁺ especially with regards to its protection against perturbation of non-enzymatic and enzymatic anti-oxidants has been investigated. Pretreatment with TQ (10 μmol·L⁻¹) demonstrates a significant protection by decrease in protein oxidation and the depleted anti-oxidants rejuvenation of cellular fraction [125]. Another study was undertaken to explore and validate *N. sativa* fixed oil (NSFO) and essential oil (NSEO) in diabetes mellitus treatment and the results supported the traditional use of *N. sativa* and its derived products as a treatment for hyperglycemia and associated abnormalities. In addition NSFO and

NSEO considerably ameliorate free radicals and improve antioxidant capacity [126]. Moreover, the protective effects of NSO supplementation against aluminium chloride-induced oxidative liver and erythrocytes damage have been evaluated in rats. NSO reduces aluminium chloride-induced oxidative injury in the liver and erythrocytes of the rats [127]. In another study, pretreatment of mice with 12.5 mg·kg⁻¹ TQ significantly reduces the elevated levels of serum enzymes as well as hepatic MDA content and significantly increased hepatic nonprotein sulfhydryl (-SH) [32]. Indeed *N. sativa* contributes to inhibition of the enzymes present in the neoglucogenesis pathway in the liver [128].

Neuro-protective activity

Effects of NSO on the central nervous system have been sedating and weakening [60]. The TQ derived from *N. sativa* extract causes a reduction in neuronal degeneration [129]. Research has shown that TQ has an effective analgesic effect [130] and exerts these effects through stimulation of opioid receptors in the central nervous system [131]. In another study, administration of intracranial TQ blocked PTZ-induced seizures and probably mediated this effect by increasing the gabaergic system tone and opioid receptors [132]. It is reported that *N. sativa* (200–400 mg·kg⁻¹) causes loss of depression in the forced swim test and open field test in the LPS-induced depression model [30]. Abdul Zahir et al. have reported that NSO can protect mice in the tolerance and dependence caused by tramadol. NSO has therapeutic potential through blocking the overproduction of drug-induced nitric oxide and oxidative stress [133].

Immuno-protective activity

Many studies have demonstrated the effect of *N. sativa* and TQ on the immune system [67, 134–135]. In one of these studies *N. sativa* products lead to a reduction in B cell-mediated immunity *in vitro* [135]. Some other studies have indicated that α-linolenic acid, estearidonic acid and other compounds of the plant seed boost the immune response, particularly T lymphocytes [136–137]. *N. sativa* increases the proportion of helper T cells to suppressor T cells and increases the activity of natural killer cells [134]. Additionally, this herb stimulates interleukin-3 secretion by T cells [138]. Moreover, the plant's positive stimulatory effect on macrophages has been reported. *N. sativa* (2 g) supplementation with immunotherapy for 30 days results in an increase in phagocytic activity of macrophages in comparison to immunotherapy alone [139]. A research has demonstrated that the use of NSO for six weeks, increases phagocytic activity of peritoneal macrophages and increases the number of peripheral blood lymphocytes in diabetic rats [99].

In an experiment on mouse spleen cells, no effect of *N. sativa* on the immune system is reported; however, in the presence of mitogen, an unknown mechanism of immunological responses is observed [136]. In another study, *N. sativa* shows modulatory effect on pro-inflammatory and anti-inflammatory cytokine secretion. *N. sativa* also modulates Th1/Th2, and partially inhibits the Th2 [140]. In another study, *N. sativa* effects on immuno-hematological indices are investi-

gated on rainbow trout and the results indicate a significant increase in serum immunoglobulin levels in the treated group [141].

In a research, a group of medicinal plants including *N. sativa* are examined for their immunomodulatory effects in BALB/c mice. The results have confirmed the immunomodulatory activity of *N. sativa*, and it may have therapeutical implications in prophylactic treatment of opportunistic infections and supportive treatment in oncological cases [142].

Wound healing activity

N. sativa seeds and oil have been found to promote wound healing in farm animals [143]. Moreover, ether extract of *N. sativa* seed applied topically onto staphylococcal-infected skin in mice improves healing by reducing total and absolute differential WBC counts, local infection and inflammation, bacterial expansion, and tissue impairment [144]. Durmus and Ceribasi have compared the effects of *N. sativa* and silver sulfadiazine (SSD) cream on healing of burn wounds in an animal model. Histopathological evaluations on the 4th, 9th and 14th days showed that burn healing was better in the *N. sativa* and SSD groups compared with the control group. Wound healing was significantly different among the groups at 4th, 9th, and 14th days [145]. In another study, the contracting ability of the wounds treated by NSO is similar to antibiotic (Baneocin). However, there is some retardation in wound treated with NSO. The closure time of the wounds for both is similar to some extent [146]. The extract from *N. sativa* shows favorable enhancement of human gingival fibroblast proliferation with accelerated wound closure, despite its non-significant effect on collagen synthesis,

compared to *Melastoma malabathricum*, *Pluchea indica*, and *Piper sarmentosum* extracts. In addition to the increased level of bFGF by up to 15% at 100 $\mu\text{g}\cdot\text{mL}^{-1}$ of *N. sativa*, a slightly better effect was observed on the expression of TGF- β . Thus, *N. sativa* shows promising wound healing properties, validating its traditional use for the healing of oral wounds [147].

Effects on reproductive system

N. sativa seeds increase the weight of reproductive organs, sperm motility and count in cauda epididymides and testicular ducts. Spermatogenesis is increased at primary and secondary spermatocyte. And there is an increase in number of female pregnant rats [148-149]. In another study to assess the effect of NSO on sperm parameters and testes in comparison with nicotine in rats, nicotine reduced sperm motility and morphology of normal and live sperms and also affected the testes histology, while NSO increased sperm quality and exhibited better testes histological features [150]. The evaluation of the role of extract of *N. sativa* on fertility potential, pituitary-testicular axis hormones and testosterone in male rats showed that there was a significant difference in testes and epididymidis weight, sperm count, ESR, DSP, blood testosterone concentration, LH and fertility index in both the lower and higher dose groups, compared to the control group [151].

Main pharmacologic effects of *N. sativa* are summarized in Table 1.

Potential mechanisms of action

According to the literature, some potential mechanisms of the *N. sativa* effects are shown in Table 2.

Table 1 Main pharmacologic effects of *Nigella sativa*

Pharmacological effects	Type of extract	The extract dose	Design of study	Main results	Ref.
Anti-bacterial activity	Etheric	25–400 $\mu\text{g}\cdot\text{mL}^{-1}$ 2 $\text{mg}\cdot\text{kg}^{-1}$	<i>In vitro</i> <i>In vivo</i>	-Plant preparations, if given with anti-bacterial drugs, would enhance their efficacy. -Ether extract eradicated localized <i>Staphylococcus aureus</i> infection in mice.	49
	Ethanollic	3–200 $\mu\text{g}\cdot\text{mL}^{-1}$	<i>In vitro</i>	-Growth of all examined pathogenic bacteria inhibited.	52
	Volatile oil	120–600 $\mu\text{g}\cdot\text{mL}^{-1}$	<i>In vitro</i>	-All the organisms under study represented strong sensitivity	50
Anti-fungal activity	Aqueous	6.6 $\text{mL}\cdot\text{kg}^{-1}$	<i>In vivo</i>	-5-fold decrease in kidney candida. -8-fold decrease in liver candida. -11-fold decrease in spleen candida.	54
	Etheric	2.5–40 $\text{mg}\cdot\text{mL}^{-1}$	<i>In vitro</i>	- Growth inhibition in eight dermatophytes clinical isolates.	55
Anti-schistosomal activity	Aqueous	0.2 $\text{mg}\cdot\text{kg}^{-1}$	<i>In vivo</i>	-Prevented most of schistosomiasis hematological and biochemical changes in mice. -Improved the anti-oxidant capacity of schistosomiasis mice.	56
	Powder	10 gr	<i>In vitro</i>	- <i>S. mansoni</i> worms number in the liver reduced. - Ova deposited number in liver and intestine reduced.	57
Antioxidant activity	Decoction	3 $\text{mg}\cdot\text{kg}^{-1}$	<i>In vivo</i>	- Blood LPO decreased. - Plasma TTM increased.	60
	TQ	5 $\text{mg}\cdot\text{kg}^{-1}$	<i>In vivo</i>	- Malondialdehyde and conjugated diene levels increased. - Increment of CAT, glutathione peroxidase, and SOD activities decreased.	65
	Oil	0.3–0.6 $\text{mL}\cdot\text{kg}^{-1}$	<i>In vivo</i>	- Serum enzymatic activities of SOD and GSH-Px improved. - Total oxidant status decreased. - Total anti-oxidant capacity increased. - Serum and tissue malondialdehyde and NO decreased.	64

Continued

Pharmacological effects	Type of extract	The extract dose	Design of study	Main results	Ref.
Anti-inflammatory activity	TQ	25–75 mmol·L ⁻¹	<i>In vitro</i>	-Synthesis of MCP-1, TNF-alpha, interleukin (IL)-1beta and Cox-2 decreased.	78
	Aqueous	500 mg·kg ⁻¹	<i>In vivo</i>	-Carrageenan-induced paw edema reduced.	130
	TQ	3 mg·kg ⁻¹	<i>In vivo</i>	-EC50 and lung lavage fluid neutrophil count increased. -LLF lymphocyte tracheal responsiveness to methacholine decreased.	79
	Ethanollic	0–2 000 µg·mL ⁻¹	<i>In vitro</i>	-Extract at 750 µg·mL ⁻¹ and higher concentrations led to: -Morphological changes in alive cells. -Reduced percentage of alive cells. -Maximum apoptosis in ACHN cells at 1 000 & 1 250 µg·mL ⁻¹ (92%) compared with L929 cells that showed maximum apoptosis at 1 500 µg·mL ⁻¹ .	90
Anti-hyperlipidemic activity	Powder	500 mg	Clinical trial	-Decrease in total cholesterol, low density lipoprotein cholesterol and triglyceride -Increased high density lipoprotein cholesterol	81
	Powder	1, 2 and 3 g	Clinical trial	-Decrease in TC, TG, and LDL-c -Elevation in HDL-c/LDL-c	82
	Oil	2.5 mL	Clinical trial	-Decrease in fasting blood cholesterol, LDL, triglyceride (TG), glucose and HbA1C levels	83
Anti-cancer activity	Oil	50–100 µg·mL ⁻¹	<i>In vitro</i>	- Plasminogen activator inhibitor-type 1 increased.	94
	TQ	20–80 µmol·L ⁻¹	<i>In vitro</i>	-NF-κB DNA-binding activity, XIAP, survivin and VEGF in SaOS-2 cells down regulated. -Expression of cleaved caspase-3 and SMAC in SaOS-2 cells upregulated.	92
	Aqueous	50 mg·kg ⁻¹	<i>In vivo</i>	-Genotoxicity and ultrastructural changes induced by doses of CCl ₄ improved.	44
Anti-diabetic activity	Oil	0.20 mL·kg ⁻¹	<i>In vivo</i>	-Elevated serum glucose decreased. -Lowered serum insulin concentrations and partial regeneration/proliferation of pancreatic β-cells increased.	102
	Aqueous	2 mL·kg ⁻¹	<i>In vivo</i>	-Tissue MDA and serum glucose decreased.	46
	Oil	0.2 mL·kg ⁻¹		-Tissue SOD and serum insulin increased.	
	TQ	3 mg·mL ⁻¹		-Normal insulin levels restored. -Failed to decrease serum glucose concentrations to normal. -Toxic effects of STZ, including segregated nucleoli, heterochromatin aggregates ameliorated.	103
Cardiovascular protective activity	Powder	<i>N. sativa</i> -mixed pelleted food (6.25%)	<i>In vivo</i>	-Lowered maximum contractile in <i>N. sativa</i> -treated group. -Prevented DEP-induced decrease in SBP and leukocytosis.	108
	TQ	6 mg·kg ⁻¹	<i>In vivo</i>	-IL-6 concentration increased. -Plasma SOD activity decreased.	110
	Aqueous	20 mL·kg ⁻¹	<i>In vivo</i>	- The elevated glucose concentration decreased. -The lowered RBC and WBC counts, PCV and neutrophil percentage increased. - The elevated heart rate decreased.	110
	Aqueous	250–500 mg·kg ⁻¹	<i>In vivo</i>	-Prevented gastric ulcer formation induced by necrotizing agents. -Ameliorated the ulcer severity and basal gastric acid secretion in pylorus-ligated Shay rats. -Replenished the ethanol-induced depleted gastric wall mucus content levels and gastric mucosal non-protein sulfhydryl concentration.	114
Gastro-protective activity	TQ	5–25 mg·kg ⁻¹	<i>In vivo</i>	-Prevented the appearance of diarrhea -Body weight loss reduced. -Colonic myeloperoxidase activity and malondialdehyde levels reduced. -Glutathione levels increased.	118
	Oil TO	2.5 and 5 mL·kg ⁻¹ 5–100 mg·kg ⁻¹	<i>In vivo</i>	-The level of LDH, GSH and SOD normalized. -Levels of lipid peroxide restored to normal. -The GSH content reduced in high doses.	117
	Powder	0.01–1 g·kg ⁻¹	<i>In vivo</i>	-Serum creatinine of high dose treated compared with low dose treated and control groups decreased.	121

Continued

Pharmacological effects	Type of extract	The extract dose	Design of study	Main results	Ref.
Nephro-protective activity	Oil	2.5–5.0 mL·kg ⁻¹	<i>In vivo</i>	-Plasma transaminase activities, hepatic MDA, and TG levels decreased. -Hepatic histopathological findings meliorated.	123
	TQ	13 µg·kg ⁻¹	<i>In vivo</i>	-Intestinal mast cell numbers and plasma mouse mast cell protease-1 (MMCP-1) decreased. -Diarrhea severity at the final challenge decreased. -No significant changes in total plasma IgE and OVA-specific IgE were observed.	125
	Oil	2 mL·kg ⁻¹	<i>In vivo</i>	-Hepatic and erythrocyte malondialdehyde level decreased. -Glutathione content, glutathione peroxidase, superoxide dismutase and catalase decreased.	127
Hepato-protective activity	Hydro-alcoholic	200–400 mg·kg ⁻¹	<i>In vivo</i>	-Caused loss of depression in the forced swim test and open field test.	30
	Oil	4 mL·kg ⁻¹	<i>In vivo</i>	-Dependence on tramadol reduced. -Overproduction of nitric oxide inhibited. -Malondialdehyde levels increased.	133
Neuro-protective activity	TQ	5 mL·kg ⁻¹	<i>In vivo</i>	-The number of dead hippocampal neuronal cells decreased. -Elevated levels of malondialdehyde decreased. -GSH contents increased. -Catalase and SOD activities normalized.	62
	Ethanollic	2 g eq plant/kg	<i>In vivo</i>	-Phagocytic activity of peritoneal macrophages increased. -Peripheral blood lymphocytes number increased.	99
Effect on reproductive system	Alcoholic	200 and 400 mg·kg ⁻¹	<i>In vivo</i>	-Increase in testes and epididymidis weight, sperm count, blood testosterone concentration, LH and fertility index	151
Immuno-protective activity	Ethanollic	200 mg·mL ⁻¹	<i>In vivo</i>	-Pro- inflammatory and anti-inflammatory cytokine secretion modulated. -Th1/Th2 modulated. -Partially inhibited the Th2.	140

TQ: thymoquinone; TTM: total thiol molecules, SBP: spontaneous bacterial peritonitis.

Table 2 The potential mechanisms of efficacy for some pharmacologic properties of *Nigella sativa*

Pharmacological effects	Possible mechanisms of efficacy	Ref.
Anti-microbial activity	Presence of active compounds with anti-microbial activity such as thymohydroquinone and melanin.	42, 47–48
Anti-oxidant activity	Presence of antioxidant compounds such as flavonoids, alkaloids, tannins, thymoquinone (TQ), carvacrol, t-anethole and 4-terpineol/Removal and trapping free radicals /Reducing MDA level/lipid peroxidation inhibition/Improvement of enzymatic and non-enzymatic activities associated with the oxidation inhibition.	61–63
Anti-inflammatory activity	Inhibition of inflammatory mediators (IL-1, IL-6), lipo-oxygenase and cyclo-oxygenase/ Macrophage iNOS enzyme inhibition by extract thymoquinone.	73, 76
Anti-hyperlipidemic activity	TQ, migellamine, soluble fiber (mucilage), sterols, flavanoids and polyunsaturated fatty acids in <i>N. sativa</i> are able to regulate cholesterol synthesis through regulation of HMG-CoA reductase, Apo-A1, Apo-B100 and LDL-receptor genes; enhancing the efficiency of liver cells to remove LDL from the blood circulation; also contributing to decrease dietary cholesterol absorption; and increasing the primary bile synthesis.	81–84
Immuno-protective activity	Strengthen the immune system by increasing macrophage activity and lymphocyte numbers/ Inhibition of inflammatory processes by thymoquinone/strengthening the immune response, especially in T cells by alpha linoleic acid, stearic acid and other <i>N. sativa</i> seed compounds.	68, 136–137
Anti-cancer activity	Presence of compounds such as saponins, thymoquinone and alpha-hederin through inhibition of cell proliferation, apoptosis induction through dependent-pathway and P53 independent, anti-oxidant activity and glutathione alternation.	85, 87–88
Anti-diabetic activity	Regulating liver enzymes activity associated with glucose metabolism; reducing gluconeogenesis; antioxidant activity; preservation and proliferation of pancreatic beta cells; and activating AMPK by TQ.	100, 106–107
Neuro-protective activity	Analgesic effect by opioid receptor stimulation; and neuronal degeneration reduction by TQ.	129–130
Hepato and nephro-protective activity	Protective effect on the liver and kidneys due to glutathione reduction and antioxidant effect by TQ.	120, 123
Wound healing activity	Enhancing the proliferation of fibroblasts and promoting the level of beta-FGF.	147
Protection of reproductive system	Prevention of cell death and loss of tissue weight or volume of sexual cells by inhibit of cyclooxygenase and lipo-oxygenase enzymes and reduce the harmful effects of free radicals.	150–151

Dosage and side effects

In a study, *N. sativa* up to 1 g·kg⁻¹ was supplemented for a period of 28 days, resulting in no changes in liver enzymes level and no toxic effects on the liver function^[121]. Also, toxicity of NSFO in mice and rats has been tested, through determination of LD50 values and examination of possible biochemical, hematological and histopathological changes. No changes are observed in the levels of key hepatic enzymes, including AST, ALT, and GGT and histopathological modifications (heart, liver, kidneys and pancreas) in treated rats. However, the serum levels of cholesterol, TG, and glucose and the count of leukocytes and platelets are decreased significantly, compared to control values, while hematocrit and hemoglobin levels are increased significantly. The results show that the low toxicity of NSFO is confirmed by high LD50 values, key hepatic enzyme stability and organ integrity. Thus a wide margin of safety for therapeutic doses of NSFO exists, but the changes in hemoglobin metabolism and the fall in leukocyte and platelet counts must be taken into consideration^[153]. Actually, large doses of NSO have toxic effects on the histological structure of the kidneys and to a lesser degree on the liver. Thus, NSO should be used in proper doses, and further studies are recommended^[154].

Conclusion

N. sativa has been considered worldwide as an important medicinal herb. Its use in pharmaceutical, food and ornamental industries displays considerable commercial value. *N. sativa* and its compounds, particularly TQ, have various pharmacological effects on different body parts. Available reports show anti-inflammatory, anti-microbial, anti-cancer, anti-oxidant, anti-diabetic, and anti-hypertensive activities of the plant. Also, its effects on digestive, immune, and central nervous system have been demonstrated in various studies. The plant composition and medicinal properties necessitate further research on other useful and unknown features, so it can be used as a plant-derived medicine to treat various diseases.

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